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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/602,521

06/24/2003

David Edwin Thurston

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MICHAEL BEST & FRIEDRICH LLP
ONE SOUTH PINCKNEY STREET
P O BOX 1806
MADISON, WI 53701

EXAMINER

GROSS, CHRISTOPHER M

ART UNIT

PAPER NUMBER

1639

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12/10/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/602,521	Applicant(s) THURSTON ET AL.	
	Examiner CHRISTOPHER M. GROSS	Art Unit 1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 September 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 39-49 and 51-63 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 39-49 and 51-63 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☒ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☒ Certified copies of the priority documents have been received in Application No. 09/763,768.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|----------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/26/2008</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Responsive to communications entered 9/26/2008. Claims 39-49,51-63 are pending. Claims 39-49,51-63 are examined herein.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/26/2008 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

This application was filed 6/24/2003 and is a CON of application 09/763,768 (referred to as '768) filed 02/26/2001 (now PAT 6,608,192) which is a 371 of PCT/GB99/02836 filed 08/27/1999.

Acknowledgment is further made of applicant's claim for foreign priority based on application no. 9818730.5 filed in the United Kingdom on 08/27/1998. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), in the parent case '768.

It is noted, however, an optional double bond between C1 and C2 such as set forth in the present claims is not disclosed in the UK application. Accordingly the earliest priority date for the present application is 8/27/1999.

Withdrawn Rejection(s)

The rejection of claims 39-49 and 51-64 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed had possession of the claimed invention is hereby withdrawn in view of applicant's amendments and persuasive arguments.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 39-49,51,53,54,55,57,58-60, 61 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Baraldi et al** (1998 Bioorganic & Medicinal Chemistry Letters 8:3019-3024 – IDS entry 12/21/2007) in view of **Baird et al** (1996 JACS 118:6141-6146).

Claim 39 is drawn to a collection of compounds represented by formula II, shown therein wherein:

Art Unit: 1639

A is O, S, NH, or a single bond;

R2 and R3 are independently selected from: H, R, OH, OR, =O, =CH-R, =CH2, CH2-CO2R, CH2-CO2H, CH2-SO2R, O-SO2R, CO2R, COR, CN and there is optionally a double bond between C1 and C2 or C2 and C3;

R6, RT, and R9 are independently selected from H, R, OH, OR, halo, nitro, amino,

Me3Sn;

where R is an alkyl group having 1 to 10 carbon atoms, or an aralkyl group of up to 12 carbon atoms whereof the alkyl group optionally contains one or more carbon-carbon double or triple bonds, which may form part of a conjugated system, or an aryl group of up to 12 carbon atoms; and is optionally substituted by one or more halo, hydroxy, amino, or nitro groups, and optionally contains one or more hetero atoms which may form part of, or be, a functional group;

Y is a divalent group such that HY = R;

X' is CO, NH, S or O;

T is an amino acid residue combinatorial unit, where each T may be different if n is greater than 1; and

n is a positive integer from 1 to 16.

Baraldi et al teach throughout the document and especially scheme 2, preparation of a pyrrolobenzodiazepine-distamycin conjugate, which reads on claims 39-49,51,53, 58,59,60,61 and 63 when: A=O; R2=R3=R6=R9=R11=H; R7 is methoxy; Y is an ethoxy chain; X' is CO and T and T'' are a N methylpyrrole amino acids; n is 1; m is 0; q is 0; R10=Troc. Please note, N methylpyrrole amino acids, such as present in distamycin are included in the definition of amino acids set forth in paragraph 0089 of the present published application.

Baraldi et al do not teach: a collection of compounds, as set forth in the preamble to claim 39,51,53,54,55,57,58,61,63; the solid support set forth in claims 54,55,57,58, 61 and 63.

Baird et al teach, throughout the document and especially figure 6, solid-phase synthesis of distamycin polyamide analogs. Said analogs are taken as a collection of compounds. Said solid phase synthesis of Baird et al includes a solid support (resin).

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to prepare various pyrrolobenzodiazepine-distamycin polyamide analogs per Baraldi et al with the solid-phase method according to Baird et al.

One of ordinary skill in the art would have been motivated to prepare various pyrrolobenzodiazepine-distamycin analogs per Baraldi et al with the solid-phase method according to Baird et al because it would circumvent challenges regarding variable coupling yields and numerous side products normally associated with preparing pyrrole polyamides in solution, as noted by Baird et al in the last paragraph on p 6141.

One of ordinary skill in the art would have had a reasonable expectation of success in preparing various pyrrolobenzodiazepine-distamycin analogs per Baraldi et al with the solid-phase method according to Baird et al because both references concern distamycin, thus the pyrrolobenzodiazepine-distamycin conjugate, prepared by Baraldi et al lies well within the scope of technology according to Baird et al.

In conclusion, the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and was as a whole, *prima facie* obvious.

Claims 52, 56 and 62 rejected under 35 U.S.C. 103(a) as being unpatentable over **Baraldi et al** (1998 Bioorganic & Medicinal Chemistry Letters 8:3019-3024 – IDS entry 12/21/2007) **in view of Baird et al** (1996 JACS 118:6141-6146) as applied to claims 39-49,51,53, 54, 55,57,58-60, 61,63 above, and further in view of Tam (US Patent 5229490)

Baraldi et al in view of Baird et al are relied on as above.

Baraldi et al in view of Baird et al do not teach the topological arrangement of amino acid combinatorial units, set forth in formulas XII,X, and XI of claims 52, 56 and 62 respectively, bearing, for instance two pyrrolobenzodiazepine groups: one on the main chain and a second on the side chain of an amino acid combinatorial unit.

Tam teaches, throughout the document and especially figure 1 and example 1, preparation of peptide dendrimers, by successive additions of Boc-Lys(Boc)-OH to a solid support. For example in example 1, after one round of coupling and deprotection of Boc-Lys(Boc)-OH, two free amines are generated: one main chain (alpha) and one side chain (epsilon) in H-Lys-beta alanine -OCH₂PAM resin.

It would have been *prima facie* obvious for one of ordinary skill in the art, at the time the claimed invention was made to derivatize H-Lys-beta alanine -OCH₂PAM resin per Tam with compound 10 of Baraldi et al, for instance, or analogs thereof, so as to generate pyrrolobenzodiazepine-Lys(pyrrolobenzodiazepine)-beta alanine -OCH₂PAM type compounds, such as set forth in claims 52, 56 and 62.

One of ordinary skill in the art would have been motivated to prepare peptide dendrimers in the manner of Tam in concert with the pyrrolobenzodiazepine-distamycin

Art Unit: 1639

analogues per Baraldi et al in view of Baird et al because, unlike other methods of preparing dendrimers, the exact structure is known, as noted by Tam in column 3 line 32, which would simplify discerning structure activity relationships.

One of ordinary skill in the art would have had a reasonable expectation of success in preparing peptide dendrimers in the manner of Tam in derivatized with the pyrrolobenzodiazepine-distamycin analogues per Baraldi et al in view of Baird et al because each reference concerns peptide synthesis, accordingly the synthetic strategy of Baraldi et al in view of Baird et al is completely compatible with that of Tam.

In conclusion, the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and was as a whole, *prima facie* obvious.

New Claim Rejection(s) – 35 USC § 112

The following is a quotation of the **second** paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51-63 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Each of claims 51,52,53,55,56,57,61-63 recite vague and indefinite language with regard to n and m. Each claim states that n **is** a positive integer from 1 to 16 and m **is** 1 except that one of n or m may be zero. It is not clear how m may be, for instance

Art Unit: 1639

both 1 and 0 simultaneously or how n can be both positive and 0, therein rendering the metes and bounds of the offending claims unascertainable.

Each of amended claim 55-57,61-63 recites the limitation "them," as amended .There is insufficient antecedent basis for "them" in the claim.

Each of claims 54-63 recite a circle with a dot in the middle as a symbol indicating a solid support but which is not shown in the formula. There is insufficient antecedent basis for said circle with a dot in the middle in the claim.

In accordance with MPEP 2173.02: If the language of the claim is such that a person of ordinary skill in the art could not interpret the metes and bounds of the claim so as to understand how to avoid infringement, a rejection of the claim under 35 U.S.C. 112, second paragraph, would be appropriate. See *Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 USPQ2d 1190, 1195 (Fed. Cir. 1993).

9The following is a quotation of the **first** paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection concerns "new matter"

Each of claims 54-63 recite a circle with a dot in the middle as a symbol indicating a solid support.

The specification as originally filed provided no implicit or explicit support for circles with a dot in the middle. Please note in addition to the concerns raised under 35 USC 112 second paragraph rejection above, it is not clear if said symbol represents *any* type of solid support or a particular species thereof.

Applicants are reminded that it is their burden to show where the specification supports any amendments to the disclosure. See MPEP 714.02, paragraph 5, last sentence and also MPEP 2163.06 I.

MPEP 2163.06 notes “If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).” MPEP 2163.02 teaches that “Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes “When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not “new matter” is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

Art Unit: 1639

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER M. GROSS whose telephone number is (571)272-4446. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571 272 0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christopher M Gross
Examiner
Art Unit 1639

cg

/ Christopher S. F. Low /
Supervisory Patent Examiner, Art Unit 1639